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Comprehensive genomic profiling for patients with chemotherapy-naïve advanced cancer

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Abstract

Comprehensive genomic profiling (CGP) testing by next-generation sequencing has been introduced into clinical practice as part of precision cancer medicine to select effective targeted therapies. However, whether CGP testing at the time of first-line chemotherapy could be clinically useful is not clear. We conducted this single-center, prospective, observational study to investigate the feasibility of CGP testing for chemotherapy-naïve patients with stage III/IV gastrointestinal cancer, rare cancer, and cancer of unknown primary, using the FoundationOne® companion diagnostic (F1CDx) assay. The primary outcome was the detection rate of at least one actionable/druggable cancer genomic alteration. Actionable/druggable cancer genomic alterations were determined by the F1CDx report. An institutional molecular tumor board determined the molecular-based recommended therapies. A total of 197 patients were enrolled from October 2018 to June 2019. CGP success rate was 76.6% (151 of 197 patients), and median turnaround time was 19 days (range: 10-329 days). Actionable and druggable cancer genomic alterations were reported in 145 (73.6%) and 124 (62.9%) patients, respectively. The highest detection rate of druggable genomic alterations in gastrointestinal cancers was 80% in colorectal cancer (48 of 60 patients). Molecular-based recommended therapies were determined in 46 patients (23.4%). CGP testing would be a useful tool for the identification of a potentially effective first-line chemotherapy.

Abbreviations: BTC, biliary tract cancer; CGP, comprehensive genomic profiling; CRC, colorectal cancer; CUP, cancer of unknown primary; EC, esophageal cancer; F1CDx, FoundationOne® companion diagnostic; FDA, Food and Drug Administration; FFPE, formalin-fixed paraffin-embedded; GC, gastric cancer; GPCR, G protein–coupled receptor; MAPK, mitogen-activated protein kinase; MBRT, molecular-based recommended therapy; MSI, microsatellite instability; MSK-IMPACT™, Memorial Sloan Kettering–Integrated Mutation Profiling of Actionable Cancer Targets; NGS, next-generation sequencing; PC, pancreatic cancer; RC, rare cancer; TAT, turnaround time; TGF-β, transforming growth factor beta; TMB, tumor mutational burden.

Clinical trial information: UMIN000034830.

KEYWORDS

actionable genomic alteration, comprehensive genomic profiling, druggable genomic alteration, gastrointestinal cancer, precision cancer medicine

1 | INTRODUCTION

Comprehensive genomic profiling (CGP) testing by hybrid capture next-generation sequencing (NGS) is now used in clinical practice to provide precision cancer medicine worldwide.[1] In the United States of America, the Oncomine™ Dx target test (Thermo Fisher Scientific) was approved by the Food and Drug Administration (FDA) in June 2017 as the first NGS-based companion diagnostic for patients with non–small cell lung cancer. The Memorial Sloan Kettering–Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT™)[2] and FoundationOne® companion diagnostic (F1CDx; Foundation Medicine, Inc) tests were subsequently approved for all solid tumors in November 2017. In Japan, the NGS-based multiplex gene assay OncoPrime™ was first introduced to clinical practice at Kyoto University in 2015.[3] Two years after the FDA's initial approval, in May 2019 the F1CDx assay and OncoGuide™ NCC Oncopanel System (Sysmex Corp.) were approved for reimbursement by the Japanese National Health Insurance system for patients with solid tumors refractory to standard chemotherapy. While the OncoGuide™ NCC Oncopanel System was indicated only for CGP, F1CDx was indicated for both companion diagnostic and CGP.

Precision cancer medicine by CGP testing originally aimed to select potentially effective targeted therapies as an initial treatment. However, the current indication of CGP in Japan is for patients with solid tumors refractory to the standard of care, or those without standard chemotherapy, resulting in a very limited number of patients having a chance to receive genomically "matched" therapies in clinical trials.[2,4,5] As the general condition of patients with cancer is usually better in the front-line setting than in later lines, targeted cancer therapies corresponding to "druggable cancer genomic alterations" could be more beneficial for patients in the first-line setting.

Although a CGP test for patients with cancer before the start of first-line chemotherapy might be clinically useful, supportive data of its effectiveness are lacking.[6,7] In the current study, we have tested the clinical significance of CGP testing in chemotherapy-naïve patients with stage III/IV gastrointestinal cancer, rare cancer, and cancer of unknown primary (CUP) by determining the rate of actionable/druggable cancer genomic alterations using F1CDx.

2 | MATERIALS AND METHODS

2.1 | Patient population and study design

This was a single-center, prospective, observational study. Key inclusion criteria were: histologically confirmed stage III/IV (UICC-TNM 8th edition) gastrointestinal cancer; rare cancer (annual incidence rate <6/100 000 and rare histologic subtype of a major cancer) and CUP; aged 16 years or above; available formalin-fixed paraffin-embedded (FFPE) cancer tissue for pathologic diagnosis and genomic sequencing stored for less than 3 years; and no prior cancer chemotherapy. Patients treated with only oral fluoropyrimidine drugs as an adjuvant therapy were eligible, if they had sufficient FFPE tissue obtained before the start of anticancer therapy. Patients were excluded if they had recurrent disease inside the irradiation field, had recurrence more than 3 years after surgery, or had no available tumor tissue. The primary outcome of this study was the detection rate of at least one actionable/druggable cancer genomic alteration using the CGP assay. Secondary outcomes were evidence-level classification and accessibility of therapeutic drugs targeting cancer genomic alterations, and turnaround time (TAT).

2.2 | CGP assay

The F1CDx assay was performed as previously described using archived FFPE tumor tissue.[8] F1CDx detects substitutions, insertions, deletion alterations, and copy number alterations in 324 genes and selected gene rearrangements, as well as genomic signatures such as microsatellite instability (MSI) and tumor mutational burden (TMB).

Assay results were divided into three categories (Figure 1): "passed," "qualified," and "failed," based on the results of the F1CDx assay. "Passed" was defined as reports with results of all items examined. "Qualified" was defined as reports which may have reduced sensitivity when the specimen does not meet performance specifications. "Failed" was defined as reports unavailable, that is, cases in which no reportable variants have been detected and one (or more) analysis metrics were not met according to the Foundation Medicine, Inc criteria.

Success rate of this assay was calculated by the ratio of the patients with "passed" or "qualified" F1CDx reports to all the patients whose FFPE tumor tissues were submitted.

TAT was defined as the interval between shipping date and the date the report was received from Foundation Medicine, Inc. The data cut-off date was December 31, 2019.

2.3 | Definition of actionable and druggable cancer genomic alterations

"Actionable cancer genomic alterations" and "druggable cancer genomic alterations" were defined based on the F1CDx report from Foundation Medicine, Inc. The report provides standardized

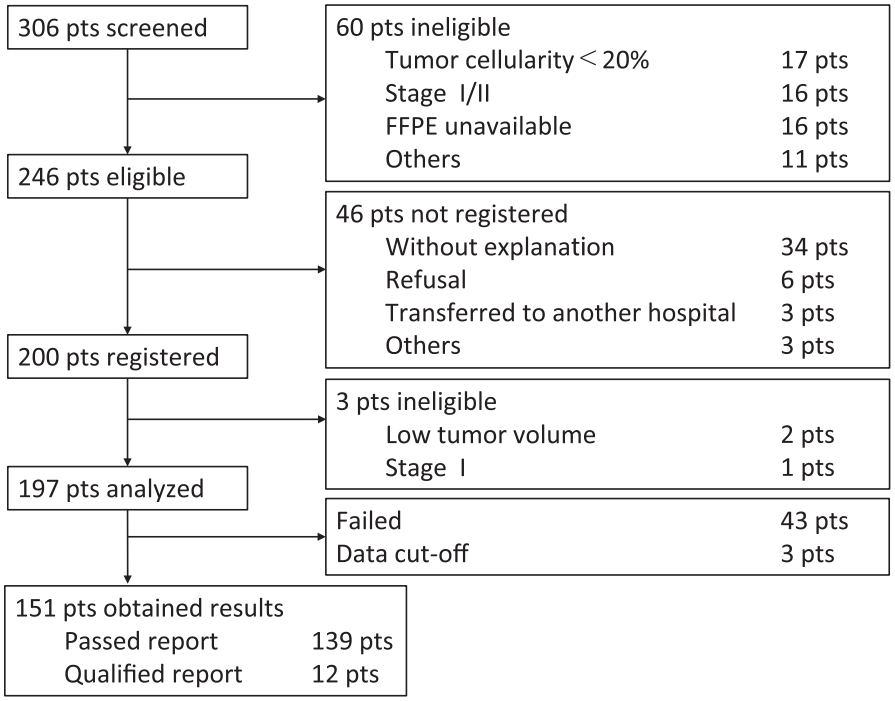

FIGURE 1 Trial profile. Passed report was defined as reports with results of all items examined. Qualified report was defined as reports which may have reduced sensitivity when the specimen does not meet performance specifications. pts, patients; FFPE, formalin-fixed paraffin-embedded.

information about companion diagnostic genomic findings, genomic signatures, and their associated targeted therapies for each patient. The scores of TMB were divided into three categories: TMB-high corresponds to greater than or equal to 20 mutations per megabase, TMB-intermediate corresponds to 6-19 mutations per megabase, and TMB-low corresponds to fewer than or equal to five mutations per megabase. We defined alterations described in the sections of "companion diagnostic–associated findings," "biomarker findings," and "genomic findings" in F1CDx report as "actionable cancer genomic alterations." If the biomarker had an available therapeutic drug, it was defined as "druggable cancer genomic alterations." In addition to these findings, clinically significant alterations described in the section of "genomic findings with no reportable therapeutic or clinical trials options" in the F1CDx report were also defined as "actionable cancer genomic alterations." Alterations reported as therapeutic resistance alone were not included in "druggable cancer genomic alterations" or "actionable cancer genomic alterations"; for example, *RAS* mutations in colorectal cancer regarding anti–epidermal growth factor receptor antibodies.[9]

2.4 | Accessibility of therapeutic drugs targeting cancer genomic alterations

Each result in the F1CDx report was carefully discussed by the molecular tumor board in our hospital, which consisted of a multidisciplinary team of medical professionals, including medical oncologists, pathologists, medical geneticists, genetic counselors, genomic researchers, and bioinformaticians. The molecular tumor board decided the molecular-based recommended therapies (MBRTs)[7] based on the druggable cancer genomic alterations.

Accessibility of the MBRT was divided into six ranks[10]: Access-1, therapies approved by Japan's National Health Insurance system for this indication; Access-2, clinical trial available in Japan; Access-3, therapies approved by Japan's National Health Insurance system for another indication; Access-4, clinical trial available outside Japan; Access-5, therapies approved by the FDA; and Access-6, others.

2.5 | Evidence level

Evidence-level classification was decided according to Clinical Practice Guidance for Next-Generation Sequencing in Cancer Diagnosis and Treatment Edition 1.0,[11] Edition 2.0,[10] and OncoKB levels of evidence V1.[12]

2.6 | Statistical analysis

Statistical analyses were performed using R version 3.5.3. (R Project for Statistical Computing).

2.7 | Ethics

The study protocol was approved by the ethics committee of Kyoto University Graduate School and Faculty of Medicine (G1156), and the study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent for the use of genomic and clinical data for research purposes. This study was registered with the UMIN Clinical Trials Registry as UMIN000034830.

3 | RESULTS

3.1 | Patient characteristics

From October 2018 to June 2019, a total of 306 patients were prescreened, and 246 patients were eligible in the study (Figure 1). Forty-six patients were not registered: 34 without explanation, six refused, three did not have FFPE tissue available, and three were not registered for other reasons. Two hundred patients were registered on the study. Three patients were excluded because of inadequate registration: low tumor volume of FFPE tissue for analysis (n = 2) and stage I (n = 1). Finally, 197 patients were analyzed in the study. Patient characteristics are summarized in Table 1. Median age was 65 years (range, 22-88 years), 108 patients (54.8%) were male, 141 had gastrointestinal cancers, and 56 had rare malignancies or CUP.

TABLE 1 Patient characteristics

	All cancers	Esophageal cancer	Gastric cancer	Colorectal cancer	Biliary tract cancer	Pancreatic cancer	Rare cancer	Cancer of unknown primary
	n = 197	n = 21	n = 19	n = 60	n = 11	n = 30	n = 53	n = 3
Age, y								
Median	65	65	68	61	68	69	64	73
Range	22-88	46-77	42-81	24-81	22-83	38-84	25-88	61-74
Gender, n (%)								
Male	108 (54.8)	15 (71.4)	14 (73.7)	30 (50.0)	8 (72.7)	13 (43.3)	27 (50.9)	1 (33.3)
Female	89 (45.2)	6 (28.6)	5 (26.3)	30 (50.0)	3 (27.3)	17 (56.7)	26 (49.1)	2 (66.7)
Smoking history, n (%)								
Yes	102 (51.8)	16 (76.2)	11 (57.9)	34 (56.7)	5 (45.5)	14 (46.7)	20 (37.7)	2 (66.7)
No	95 (48.2)	5 (23.8)	8 (42.1)	26 (43.3)	6 (54.5)	16 (53.3)	33 (62.3)	1 (33.3)
Stage (UICC 8th), n (%)								
III	67 (34.0)	9 (42.9)	6 (31.6)	19 (31.7)	4 (36.4)	12 (40.0)	17 (32.1)	0
IV	130 (66.0)	12 (57.1)	13 (68.4)	41 (68.3)	7 (63.6)	18 (60.0)	36 (67.9)	3 (100)
Metastatic site, n (%)								
Brain	2 (1.0)	1 (4.8)	0	0	1 (9.1)	0	0	0
Lung	45 (22.8)	5 (23.8)	0	14 (23.3)	3 (27.3)	7 (23.3)	15 (28.3)	1 (33.3)
Pleural	36 (18.3)	2 (9.5)	8 (42.1)	12 (20.0)	2 (18.2)	5 (16.7)	6 (11.3)	1 (33.3)
Liver	59 (29.9)	2 (9.5)	5 (26.3)	25 (41.7)	4 (36.4)	5 (16.7)	18 (34.0)	0
Peritoneal	36 (18.3)	2 (9.5)	8 (42.1)	12 (20.0)	2 (18.2)	5 (16.7)	6 (11.3)	1 (33.3)
Extra regional lymph node	48 (24.4)	9 (42.9)	5 (26.3)	15 (25.0)	3 (27.3)	5 (16.7)	10 (18.9)	1 (33.3)
Bone	17 (8.6)	1 (4.8)	2 (10.5)	1 (1.7)	0	4 (13.3)	9 (17.0)	0
Others	15 (7.6)	1 (4.8)	2 (10.5)	3 (5.0)	0	0	7 (13.2)	2 (66.7)
Tumor tissue collection method, n (%)								
Surgery	92 (46.7)	0	8 (42.1)	36 (60.0)	2 (18.2)	7 (23.3)	36 (67.9)	3 (100)
Biopsy	105 (53.3)	21 (100)	11 (57.9)	24 (40.0)	9 (81.8)	23 (76.7)	17 (32.1)	0
Tumor histology, n (%)								
Adenocarcinoma	127 (64.5)	1 (4.8)	17 (89.5)	60 (100)	11 (100)	27 (90.0)	8 (15.1)	3 (100)
Squamous cell carcinoma	22 (11.2)	18 (85.7)	0	0	0	1 (3.3)	3 (5.7)	0
Others	48 (24.4)	2 (9.5)	2 (10.5)	0	0	2 (6.7)	42 (79.2)	0
Treatment history, n (%)								
Surgery	77 (39.1)	0	9 (47.4)	33 (55.0)	2 (18.2)	7 (23.3)	24 (45.3)	2 (66.7)
Adjuvant chemotherapy	1 (0.5)	0	0	0	0	1 (3.3)	0	0
Radiotherapy	3 (1.5)	0	0	0	0	0	3 (5.7)	0

3.2 | CGP success rate and TAT

CGP data were obtained for 151 patients (success rate, 76.6%). Of these, a "passed" report and "qualified" report were obtained for 139 and 12 patients, respectively (Figure 1). CGP success rates in surgical specimens and biopsy specimens were 94.6% and 61.0%, respectively (Table 2). The median TAT was 19 days (range, 10 to 329 days). The longest TAT (329 days) was caused by insufficient tissue material for F1CDx assay. After resubmission of the tissue sample, repeated discussion was required with the laboratory regarding the sample quality. Therefore, the report was issued after the data cut-off date.

3.3 | Actionable/druggable cancer genomic alterations

Among the 197 patients, actionable cancer genomic alterations and druggable cancer genomic alterations were observed in 145 (73.6%) and 124 (62.9%) patients, respectively. Detection rates of at least one actionable/druggable cancer genomic alteration according to tumor type are shown in Figure 2. Druggable cancer genomic alterations were frequently observed in CUP (3 of 3 patients [100%]), colorectal cancer (48 of 60 patients [80.0%]), pancreatic cancer (19 of 30 patients [63.3%]), and gastric cancer (12 of 19 patients [63.2%]). On the other hand, the frequency of druggable cancer genomic alterations was relatively low in esophageal cancer (5 of 21 patients [19.0%]).

The frequency of representative druggable cancer gene alterations is shown in Figure 3. Overall, 264 druggable cancer gene alterations were reported in 197 patients. The top three most frequently altered genes were *KRAS* (a total of 50 druggable alterations), *PIK3CA* (15 alterations), and *RNF43* (12 alterations).

TABLE 2 Success rates of comprehensive genomic profiling

	n	Obtained results, n (%)
Total	197	151 (76.6)
Surgical specimen		
Total	92	87 (94.6)
Surgical specimen	76	76 (100)
Surgical specimen, excisional biopsy	16	11 (68.8)
Biopsy		
Total	105	64 (61.0)
Biopsy forceps, gastrointestinal endoscopy	61	36 (59.0)
Biopsy forceps, bile duct biopsy	7	3 (42.9)
Biopsy forceps, others	4	3 (75.0)
Needle biopsy, EUS-FNA	22	15 (68.2)
Needle biopsy, liver biopsy	7	4 (57.1)
Needle biopsy, others	4	3 (75.0)

Abbreviations: EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration.

3.4 | TMB and MSI status

In the 139 patients with available results for MSI status and TMB, three had MSI-high status and four patients had TMB-high status (Figure S1). Among them, two showed both MSI-high and TMB-high results. One patient with TMB-high and stable microsatellite status had the pathogenic variant of *POLE* R1556L. No causal variants of hypermutation were identified in another patient with TMB-high and stable microsatellite status, although the tumor had a variant of unknown significance of *POLE* R1371Q.

3.5 | MBRTs

The molecular tumor board proposed MBRTs for 46 of the 197 patients (23.4%) (Figure 2). Evidence levels[11] for the MBRTs were 1A (n = 5), 1B (n = 7), 2A (n = 3), 2B (n = 14), 3A (n = 16), and 3B (n = 1) (Table S1). MBRTs were determined based on biomarkers such as *ALK* (n = 1), *BAP1* (n = 1), *BRAF* (n = 3), *BRCA2* (n = 2), *BRIP1* (n = 1), *CDK4* (n = 1), *CTNNB1* (n = 1), *EGFR* (n = 1), *ERBB2* (n = 5), *FGFR1* (n = 1), *FGFR2* (n = 2), *FLT3* (n = 1), *HRAS* (n = 4), *IDH1* (n = 2), *KIT* (n = 2), *KRAS* (n = 3), *MET* (n = 2), MSI-high (n = 3), *NF1* (n = 2), *NTRK* (n = 1), *PALB2* (n = 1), *PTEN* (n = 1), *ROS1* (n = 1), *STK11* (n = 2), and TMB-high (n = 2) (Table S1).

Accessibility of the MBRTs were Access-1 (n = 6), Access-2 (n = 6), Access-3 (n = 26), Access-4 (n = 2), Access-5 (n = 1), and Access-6 (n = 5), respectively (Table S1).

Among the 46 patients, five had more than two MBRTs (Table S2). In three patients with colorectal cancer, two patients (ID: 5086 and 5197) had both MSI-high and other biomarkers with similar evidence level (*BRAF V600E* or *NTRK* fusion). In addition, two patients' tumors had a *BRCA2* frameshift mutation and could be matched to poly(ADP-ribose)polymerase inhibitors such as olaparib. A patient with submandibular gland cancer (ID: 5105) had a tumor with a *BRCA2* mutation and TMB-high status. One patient with a rectal gastrointestinal stromal tumor (ID: 5124) had a *KIT* mutation and an *NTRK1* rearrangement, which could lead the patient to treatment with entrectinib.

3.6 | F1CDx report and molecular tumor board

The presence or absence of recommended therapies by the original F1CDx report (druggable cancer genomic alterations) and by the molecular tumor board is shown in Table 3, with comparisons across different tumor types. Forty-five patients (22.8%) had the same MBRT between the original F1CDx report and the institutional molecular tumor board, and one patient with rare cancer (0.5%; ID: 5171) had druggable cancer genomic alterations without any recommendations by original F1CDx reports but had MBRTs by our institutional

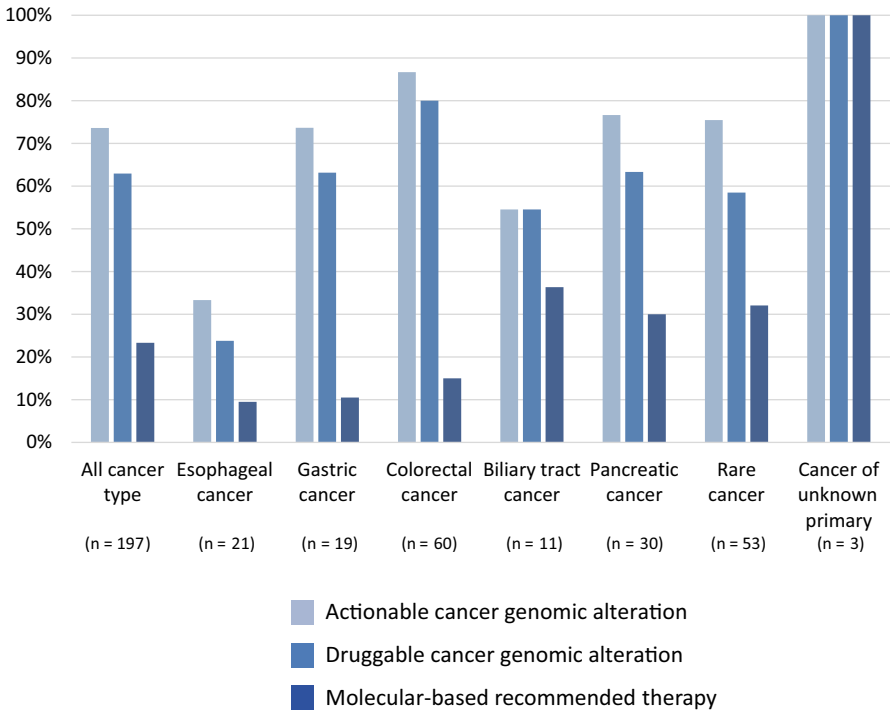

FIGURE 2 Detection rate of actionable/druggable cancer genomic alterations and molecular-based recommended therapies

molecular tumor board (Table 3 and Table S1). Twenty-six patients (13.2%) had no MBRT in either the original F1CDx report or the institutional molecular tumor board. In contrast, our institutional molecular tumor board reversed the recommendation of the original F1CDx report in 80 patients (40.6%). Seventy-nine patients (40.1%) did not have any MBRTs by our institutional molecular tumor board, while the original F1CDx report recommended MBRTs. Most of these cases were associated with *PIK3CA* (n = 8) and *KRAS* (n = 7) mutations and *PTEN* loss (n = 5).

4 | DISCUSSION

This is the first study to investigate the frequency of actionable/druggable cancer genomic alterations in chemotherapy-naïve patients with stage III/IV gastrointestinal cancer, rare cancer, and CUP, using the F1CDx assay in Japan. As a result, actionable cancer genomic alterations, druggable cancer genomic alterations, and MBRTs were found in 73.6%, 62.9%, and 23.4% of patients, respectively. These results are clinically important because more than half of patients had druggable cancer genomic alteration and one-quarter of patients with advanced cancer potentially had a chance to access a genomically "matched" treatment based on CGP testing before starting standard chemotherapy.

Until now, several clinical trials accessing CGP testing have been reported in Japan. However, they targeted patients with solid tumors refractory to the standard of care or those without standard chemotherapy.[4,5] In patients with cancers refractory to standard chemotherapy, the use of molecularly targeted agents outside the indications did not improve progression-free survival in the SHIVA trial.[6] On the other hand, when patients both refractory and not refractory to standard chemotherapy were included, MBRT was reported to improve survival.[13] Theoretically, multi-line chemotherapies induce resistance to chemotherapeutic agents. Therefore, CGP testing should be introduced at the time of first-line chemotherapy. To investigate whether CGP testing will be beneficial for chemotherapy-naïve patients, a prospective large-scale basket trial is needed.

Regarding the MBRT, several studies have been reported.[2,5,14] A prospective clinical trial using MSK-IMPACT™ reported that 11% of patients were enrolled to genetically matched clinical trials.[2] In Japan, Sunami et al reported that 13.4% of chemotherapy-refractory patients received molecular-targeted therapy according to their gene aberrations.[5] According to a report from Johns Hopkins University, 24% of patients having CGP analysis were recommended for "gene-matched" therapy as an off-label use.[14] The current study showed that 23.4% of the chemotherapy-naïve patients with stage III/IV gastrointestinal cancer, rare cancer, and CUP had a potential to access MBRT. This result encourages us to indicate CGP testing at the time of first-line chemotherapy.

However, more than half of the MBRTs in this study were not approved in Japan but can be used as off-label or investigational drugs in clinical trials. Pishvaian et al reported that patients with pancreatic cancer with actionable molecular alterations who received a matched therapy had significantly longer median overall survival than patients who only received unmatched therapies.[15] This study included patients who were treated by off-label drugs or investigational drugs in clinical trials. In order to introduce precision cancer medicine effectively into clinical practice, accessibility of anticancer drugs should be improved.

The success rate and TAT of CGP testing is particularly important when we use it in the front-line setting for patients with cancer. In this study, the CGP success rate in biopsy specimens was

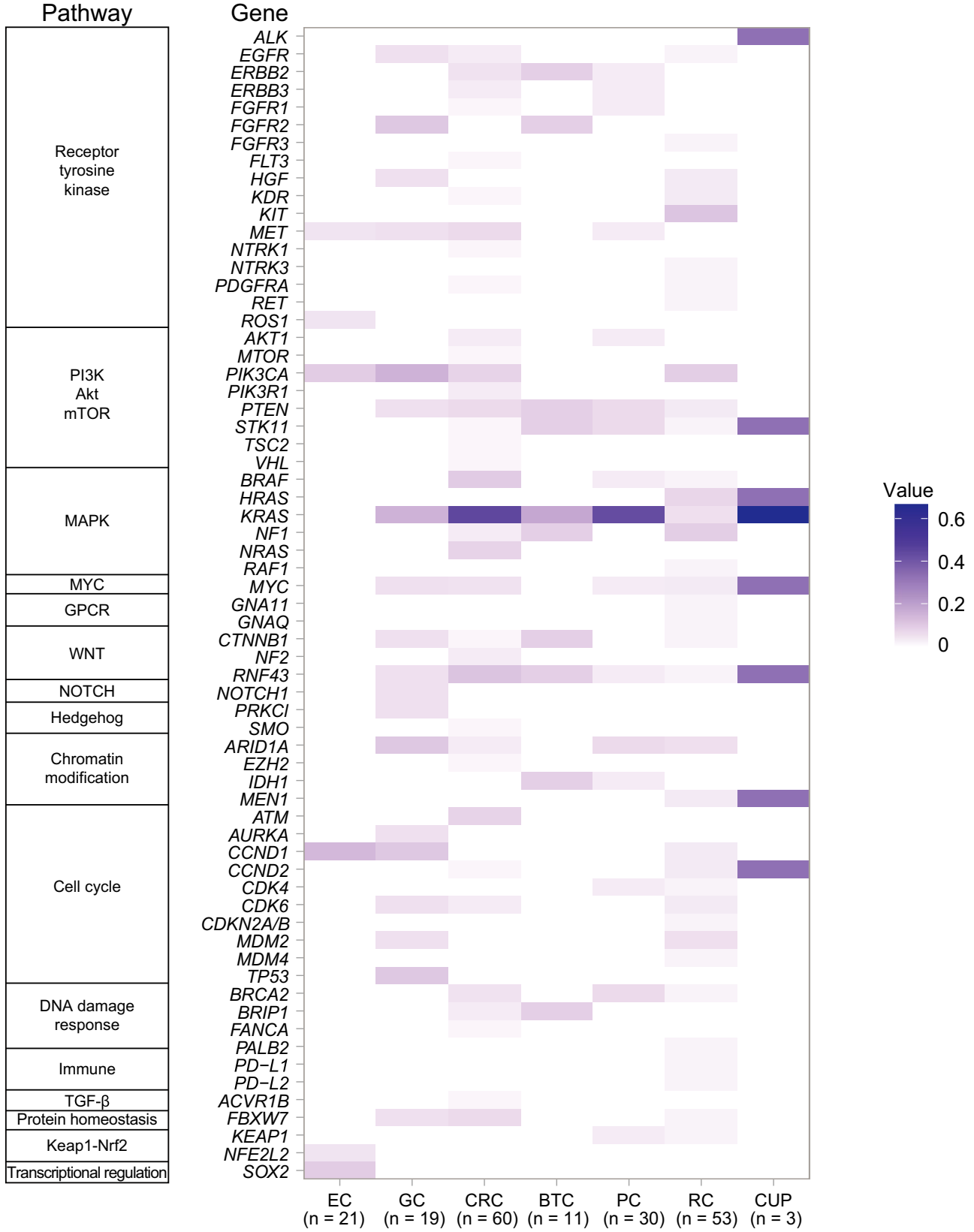

FIGURE 3 Frequency of representative druggable cancer genomic alterations. The vertical axis shows the list of representative druggable cancer genomic alterations categorized by the pathway analysis. The heatmap value represents the frequency of "number of druggable cancer genomic alterations" divided by "number of patients" in each cancer type. BTC, biliary tract cancer; CRC, colorectal cancer; CUP, cancer of unknown primary; EC, esophageal cancer; GC, gastric cancer; GPCR, G protein–coupled receptor; MAPK, mitogen-activated protein kinase; PC, pancreatic cancer; RC, rare cancer; TGF-β, transforming growth factor beta.

TABLE 3 Agreement between treatments identified based on the original F1CDx report and the molecular tumor board

Treatment identified		All cancers	Esophageal cancer	Gastric cancer	Colorectal cancer	Biliary tract cancer	Pancreatic cancer	Rare cancer	Cancer of unknown primary
Original F1CDx report	Molecular tumor board	n = 197	n = 21	n = 19	n = 60	n = 11	n = 30	n = 53	n = 3
Yes	Yes	45	2	2	9	4	9	16	3
Yes	No	79	3	10	39	2	10	15	0
No	Yes	1	0	0	0	0	0	1	0
No	No	26	2	3	4	0	4	13	0
Test failed		46	14	4	8	5	7	8	0

Abbreviations: F1CDx, FoundationOne companion diagnostic.

low compared with a previous report.[5] However, biopsy methods varied among studies and the obtained tumor volumes were also different among the methods. In addition, the CGP success rate in biopsy specimens was low compared with surgical specimens in this study. These results indicated that tumor volume might be associated with low success rate in biopsy specimens. To improve the success rate in biopsy specimens, we have to establish the reason.

Based on clinical guidelines of molecular biomarker tests such as *EGFR*,[16] *RAS*,[17,18] *ALK*,[16] and *BRAF*[17] before first-line treatment, the appropriate TAT is considered to be within 10 working days. In the current study, some cases extended TATs longer than 4 weeks, and even the shortest TAT needed 10 days. The main reason why TAT exceeded 4 weeks was due to repeated communications regarding proper sample (eg, retransportation of FFPE materials, failure of reanalysis, etc.). For utilizing the CGP test in the first-line setting, a longer TAT is not acceptable. A shorter TAT of CGP tests would be essential for chemotherapy-naïve patients with advanced cancer to receive MBRTs.

Our molecular tumor board was able to obtain appropriate treatment options, including ones not written in the original F1CDx reports by computational analysis. The proportions of the clinical evidence levels observed in this study were similar to those in previous reports,[4,5,19-21] indicating that our molecular tumor board could provide appropriate clinical judgments. Some MBRTs were not included in the F1CDx report due to the annotation process: Updates of the database and treatment guidelines occurred during the study period (Table S1). The main reason for the changes was that the latest scientific knowledge was not reflected in the F1CDx report, such as a *KRAS*-G12C inhibitor,[22] isocitrate dehydrogenase-1 inhibitor,[23] and a farnesyltransferase inhibitor.[24] After considering the latest research results, the patients' medical history, and general condition, along with F1CDx reports, our molecular tumor board recommended MBRTs in 23.4% of patients. This result emphasized the importance of the molecular tumor board.

The limitations of this study are as follows. First, as it was conducted at a single institutional academic hospital, a potential selection bias cannot be excluded. Second, this study did not include evaluation of the treatment effects of the MBRTs. We need another study to validate the clinical significance of MBRTs as the first-line chemotherapy for cancer patients. Finally, we did not include a discussion of secondary findings,[25] which will be reported separately.

In conclusion, a CGP test could be feasible in Japanese clinical practice for chemotherapy-naïve patients with advanced gastrointestinal malignancies, rare cancers, or CUP. A CGP test might be a useful tool to identify a potentially effective first-line treatment, which will lead to the establishment of precision cancer medicine. We are currently planning a prospective trial to validate the results of the current study and to further explore the potential of precision medicine for chemotherapy-naïve cancer patients.

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DISCLOSURES

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DATA AVAILABILITY STATEMENT

Clinical data of patients in our study are not available for data sharing.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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